UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/315,355	05/17/99	KEESEE	S	MTP-023DV2

EXAMINER	
HUNT, J	
ART UNIT	PAPER NUMBER
1642	7

021323 HM12/0228
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DATE MAILED: 02/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/315,355	Applicant(s) Keesee et al.
	Examiner Jennifer Hunt	Group Art Unit 1642

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *24, 25, and 39-54* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *24, 25, and 39-54* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 28-43 have been renumbered as 39-54.

Election/Restriction

2. Applicant's election of Group III in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Acknowledgment is made of applicant's cancellation of claims 26 and 27, and addition of new claims 28-43, which have been renumbered under Rule 1.126 as claims 39-54.

Claim Rejections - 35 U.S.C. § 112

4. Claims 24-25 and 39-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to detection of a nucleic acid molecule encoding a peptide of any size which is only defined by a small number of amino acid resides, hence the claims are drawn to amino acid residues which minimally contain only portions of SEQ ID NO:10. Thus the claims are drawn to a large genus of molecules. In the case of nucleic acid molecules of any length (claimed with open language) which encode small identified amino acid residues, the genus of the polynucleotides comprising a partial sequence encompasses a variety of subgenera with widely varying attributes. The specification discloses only the structural features of one species, the polypeptide of SEQ ID NO: 10 and fragments thereof, SEQ ID NO: 1-9. The specification lacks information to lead one of ordinary skill in the art to understand that the applicant had possession of the broadly claimed genus of nucleic acid molecules, or methods of using said molecules for detection at the time the instant application was filed. Applicant is referred to the interim guidelines 112, first paragraph, published in the Official gazette and also available on www.uspto.gov.

5. Claims 24-25 and 39-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

a.The instant claims are drawn to detecting cervical carcinoma by detecting the presence of a nucleic acid molecule which encodes an amino acid sequence of any of SEQ ID NO:1-10. The specification teaches detecting cervical cancer by detecting the presence of a polypeptide or specific fragments thereof which correspond to SEQ ID NO:1-10. The specification fails to teach detection of cervical carcinoma by detecting the presence of a nucleic acid molecule. Those of skill in the art, recognize that expression of a polypeptide or protein does not necessarily correlate to mRNA levels, or nucleic acid levels in general.

The following provides examples of cases where expression levels of polypeptide and nucleic acid molecules, and the conclusions which may be drawn from such are different, due to the numerous homeostatic conditions which affect transcription and translation: Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin

mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be over expressed in CHO cells following exposure to radiation, without any concomitant over expression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene.

Thus, there is no predictable correlation between protein translation and nucleic acid or mRNA expression, due to the multitude of factors affecting transcription and translation. Therefore, one of skill in the art would not be able to predict if the nucleic acid which encodes SEQ ID NO:1-10 would be correlative to cervical cancer detection, merely based on the demonstration that some cervical cancer cells express the amino acid sequences of SEQ ID NO: 1-10. The teachings in the specification are an invitation to experiment, with no clear correlation

or guidance as to how one of skill in the art could reasonably conclude that the nucleic acid molecules encoding SEQ ID NO:1-10 are useful for detecting cervical cancer.

b.The instant claims are drawn to detecting cervical carcinoma by detecting the presence of a nucleic acid molecule which encodes any of 10 amino acid sequences. The breadth of the claims encompasses variants due to degeneracy of the genetic code, and further includes any nucleic acid of any length, encoding any amino acid sequence, of any length, providing that the small fragments of SEQ ID NO:1-9 are included. The specification teaches detecting cervical cancer by detecting the presence of a polypeptide. The specification fails to teach detection of cervical carcinoma by detecting the presence of a nucleic acid molecule, and further fails to teach detection of cervical cancer by detecting variants of polynucleotides encoding SEQ ID NO: 1-10, or the peptides themselves. Thus the claims include variants and full length molecules which would fail to predictable correlate to cervical cancer, or to the polypeptides which they are supposed to encode.

The following is cited to demonstrate the lack of predictability in determining function when substitutions or fragments of nucleic acids are used: Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is

extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases

is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3).

Thus as set forth above, one of skill in the art would not be enabled to practice the invention as claimed. The claims are drawn to detecting a nucleic acid molecule to detect cervical cancer. The nucleic acid molecule can be of any length, and contain numerous substitutions (based on the degeneracy of the genetic code). The teachings of the specification relied upon for enablement are insufficient because they merely correlate detection of polypeptides to cervical cancer. The specification fails to test or determine if the nucleic acid molecules encoding those polypeptides also correspond to cancer, and further the specification fails to address that many of the nucleic acid molecules which might encode the cited SEQ ID NO:1-10 would likely not even exist in the cervical cell samples. Thus one of skill in the art would not be enabled to practice the invention as claimed.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

February 26, 2001